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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/748,055 | 12/31/2003 | Yoko Motoda | 1686-0108P | 8334 |

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| EXAMINER | |
|---|---|
| AKHAVAN, RAMIN | |
| **ART UNIT** | **PAPER NUMBER** |
| 1636 | |

DATE MAILED: 09/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/748,055 | MOTODA ET AL. | |
| | Examiner | Art Unit | |
| | Ramin (Ray) Akhavan | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *09 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *14-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/09/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.



S-S

## DETAILED ACTION

Receipt is acknowledged of a response, filed 06/09/2005, amending claims 14-17, 22-23 and 32-33. Claims 14-33 are pending and under consideration in this action.

All objections/rejections not repeated herein are hereby withdrawn. Where applicable, a response to Applicant's arguments will be set forth immediately following the body of any objections/rejections repeated herein. Any new grounds of rejection are necessitated by material changes to the claims, thus **this action is made FINAL**.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

This is a new ground of rejection necessitated by material changes to the claims. Claim 22 recites the limitation "the template". The claim is vague and ambiguous, because base claim 17 recites two different templates (i.e., first in part *i* and second in part *ii*). Thus, it is unclear to which template claim 22 is referring.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent;
or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. **Claims 14-19, 21, 23-25 and 32-33 rejected under 35 U.S.C. 102(b) as being anticipated by Lanar et al. (WO 92/07949; see whole document).**

This rejection is of record and repeated herein. A response to Applicant's argument is set forth immediately following the body of this rejection. Generally the claims are directed to a cell-free or *in vitro* process of protein production utilizing PCR generated template. The action steps or components for the claimed methods are interpreted as broadly as reasonable considering all claims are delimited using open language (i.e., *comprising*).

In other words, the steps or components are not temporally or spatially delimiting. More particularly, the claims are directed to methods of amplifying DNA fragments comprising a template DNA, a first sense primer and a second sense primer containing 3' terminal sequence that is the same as the 5' region of said first primer and a third antisense primer (claim 14). Additional claims are directed to the method comprising a template mixture of a first, second and third fragment (concentrations from 5 to 2,500 pmol/L), as well as the aforementioned primers, where the second and third fragment have overlapping regions 5' and 3' respectively to the first DNA fragment (claim 15). Furthermore, with respect to the limitations of 3' or 5' terminal sequence, the region defined as terminal sequence is interpreted as broadly as reasonable in light of the non-exclusive teaching provided in the specification (p. 6, last ¶ bridging to p. 7;

indicating the 5' primer may have "a sequence common to a part of the 5' terminal side [of the other sense primer..." Therefore, even a short nucleotide sequence (e.g., two nucleotides) that overlaps as between a first and second sense primer, meets the required claimed limitation of a "second sense primer which has a 3' terminal sequence that is the same as at least a 5' portion of the first sense primer". (e.g., claim 14).

Lanar et al. teach a method utilizing expression PCR to produce templates for *in vitro* protein production. More particularly, the reference teaches that at least two sense primers are used, as well as two antisense primers. (e.g., Figs. 5-6; pp. 10-11, Example 1; p. 12, Example 2). Furthermore, the sense primers would have at least a single nucleotide sequence in common. The reference teaches that primers A (sense primer) and B (antisense primer) are used to amplify the gene to be expressed. (e.g., p. 5, l. 11). In addition, Primer A has nucleotides at it s 5' end complimentary to the 3' end of the universal promoter (i.e., primers UP-1, UP-2 and UP-3), which also contains transcription/translation regulatory elements such as the T7 promoter element, including untranslated leader sequence necessary for ribosome binding. (e.g., Figs. 1-3; p. 5, ll. 17-20). Further, the primers are used at a concentration of 50 pmol/100ul (i.e., 500 nM; claim 19), which falls in the delimited range. (e.g., p. 13, l. 7). The antisense primer would

The reference also teaches that a third DNA fragment has a 3' region that is complementary to the 5' region of a second DNA fragment. (e.g., Fig. 6, boxed portion, depicting fragment "UTL" and unlabeled fragment, with arrows depicting 5' to 3' direction). The reference teaches that the multiple DNA segments (segment 1, 2 and 3) are used in a two-step PCR process utilizing two sense and an antisense primer (primers A, B and C) to produce one amplicon comprising portions of all the segments (claims 17 and 23). Therefore, the second

and third fragments can be single stranded, but even if double stranded initially, the fragments would be single stranded due to melting (claim 24).

The amplification of the overlapping segments along with the template encoding the gene of interest is at least for a portion of time (15 cycles) performed with no first or second sense primer and no antisense primer. (e.g., p. 13, Example 3, bridging to p. 14). As such, the primer-dimer and the primer of the two sense and an antisense primer concentrations would be less than 20nM owing to the gel purification to remove said primers (claims 18 and 21). In addition, the reference teaches that the PCR-generated templates are transcribed and translated into protein products (claims 32 and 33). (e.g., pp. 14-16, Examples, 4-5; Fig. 7). In sum, Lanar et al. anticipate the rejected claims.

***Response to Arguments***

Applicant's arguments filed 06/09/2005 have been fully considered but they are not persuasive. Applicant appears to assert primarily two arguments which are summarized as follows: (1) Lanar does not teach using a single reaction mixture (Remarks, p. 13, ¶ 2); and (2) Lanar does not teach that one of the 5' and 3' primers that are used are independent of the sequence of the cloned DNA to be amplified (Remarks, p. 13, ¶ 4; p. 14, lat ¶).

As to the first assertion, Applicant is presumably referring to the portion of the preamble (e.g., claims 14, 15, 17) or the body of the claims (e.g., claims 32-33) that recites the limitation "using a reaction solution *comprising*". (emphasis added). Applicant implies that said limitation must be construed to mean exclusively that a single reaction solution is utilized. The issue is not whether additional reaction mixtures are present, but whether at some point a single reaction solution is present that comprises the claimed structural components/elements of primers and

template DNA. Thus, if at any time during a PCR amplification process, a single reaction solution comprises the claimed components/elements, then the claimed limitation is met. Lanar does teach two reaction solutions, but the second reaction mixture comprises all the claimed limitations. (Supra, Figures 5-6; pp. 10-11, Example 1; p. 12, Example 2). In other words, since the second reaction mixture comprises the components of the first reaction solution and the second reaction solution, in effect, the resulting second solution necessarily comprises all the claimed components/elements *and* is a single solution mixture. The fact of the matter is that all the rejected claims recite open language (i.e., comprising) in delimiting "a reaction solution". Thus, if at any time during an amplification/*in vitro* protein synthesis, as taught by Lanar, a reaction solution comprises the claimed components (e.g., template, primers, etc.), then the claimed limitation is met.

With respect to Applicant's second argument, Applicant appears to be arguing limitations that are simply not present in the claims. Particularly, with respect to independent claims 15, 17 and 32, Applicant asserts that only one of the 5' primers includes a sequence that is dependent upon the sequence of the DNA template to be amplified, thus implying that said primer cannot have any sequence that is specific to the template sequence. In examining the claims, it appears Applicant is referring to *a sense primer, which anneals with the 5' terminal region of the second DNA fragment* (e.g., claim 15, part *b*), when referring to "the 5' primer" that excludes any sequence specific to the DNA template. Again, it is respectfully pointed out that the claims are broadly written with the open transitional phrase *comprising*. However, irrespective of the open language, it does not appear any language is present in the claims that can be construed to mean what Applicant suggests: that additional primers (e.g., 3' primer) cannot have sequences specific

to the template DNA. Essentially, Applicant's contention is that as written, the additional primer(s) consist of a negative limitation (i.e., no sequences specific to template DNA), which is simply not supported by the claims in their instant form. In sum, because of the instant claim language, a single reaction solution meets the claimed limitation "a solution comprising" and without temporal/spatial limitations, if the necessary components/elements are present. Further, as written the claims do not preclude additional primers from containing sequences specific to the template DNA fragment.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. **Claims 14-28, 30 and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lanar et al. (WO 92/07949), and further in view of Rothschild et al. (US 6,303,337; hereinafter the '337 patent).**

This rejection is of record and repeated herein. A response to Applicant's arguments is set forth immediately following the body of this rejection. The claims are interpreted consonant with what is stated above. In addition, the teachings of Lanar et al. are applied consonant with what is stated above. Additional claims are directed to either the second DNA fragment or the third DNA fragment comprise a sequence encoding a tag peptide, such as comprising the histidine tag peptide (i.e., 5' or 3' primer to produce a template with a C-terminal or N-terminal tag). The specification indicates that such peptides can be used in affinity separation/purification of the nascent protein.

Lanar et al. does not teach utilization of tag peptides, nor that tag peptides can consist of the native His tag peptide (i.e., SEQ ID NO: 1). However, use of affinity tags, such as His tags for purification of proteins is a well-recognized teaching in the art.

For example, the '337 patent teaches use of c-terminal and n-terminal His tag affinity markers for separation/purification of nascent proteins in a cell-free protein synthesis system. (e.g., Abstract). In addition, the '337 teaches that PCR can be used to design templates for expression in *in vitro* or *in vivo* protein expression systems, utilizing primers that contain the necessary structures/sequences for expression, such as ribosome binding sites in a prokaryotic system. (e.g., col. 9, last ¶; col. 26, last ¶ bridging to col. 27). More particularly, the reference teaches that PCR primers can be designed to incorporate affinity tags in the n- or c-terminal regions of a target protein to be expressed from a given template. (e.g., col. 27, ll. 45-65,

bridging to col. 28, ¶ 1; col. 70; Example 21; col. 70, ll. 25-45; col. 72, Example 22). Furthermore, the '337 patent teaches that the His tag marker can be used. (e.g., col. 10, ¶ 1; col. 72, l. 33).

It would have been obvious to modify the PCR methods to produce a template as taught by Lanar et al. with the PCR methods taught by the '337 patent, teaching use of primers to encode affinity tagged nascent proteins, to produce a template DNA that is used in *in vitro* protein synthesis, as is contemplated by the instant disclosure. One of ordinary skill in the art would have been motivated to make such a modification to obtain the benefit of nascent protein purification/separation as the '337 patent suggests.

Given the level of skill in the art with respect to PCR, producing fusion templates and expressing proteins in an *in vitro* system, there would have been a reasonable expectation of success in incorporating the n-terminal and c-terminal primers as taught by the '337 patent into the PCR method taught by Lanar et al. to produce DNA templates encoding proteins that are amenable to cell-free expression.

***Response to Arguments***

Applicant's arguments have been fully considered but they are not persuasive. Applicants have not presented any new arguments and rely on the arguments discussed above. (Supra, Rejection No. 2). The arguments traversing the grounds of rejection based on Lanar's teachings are addressed above and incorporated herein. Therefore, this rejection is maintained.

4. **Claims 14-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lanar et al. (WO 92/07949) and Rothschild et al. (US 6,303,337; hereinafter the '337 patent), further in view of Tchaga et al. (WO 99/57992; see whole document).**

This rejection is of record and repeated herein. A response to Applicant's arguments are set forth immediately following the body of this rejection. The claims are interpreted consonant with what is stated above. Further, the teachings of Lanar et al. and the '337 patent are applied consonant with what is stated above. Additional claims are directed to the His tag as being the native His tag (i.e., SEQ ID NO: 1).

Neither Lanar et al. or the '337 patent explicitly teach that the native His tag can be utilized in utilizing primers encoding said tag in a PCR reaction to produce a DNA template.

However, Tchaga et al. teach that the metal ion binding native His tag can be used in isolating/purifying proteins. (e.g., Abstract; pp. 10-11, Example 1). More particularly, the reference teaches the sequence for the native His tag to be used in producing DNA templates that can be used to express the tagged protein and that the tag can be placed on either the c- or n-terminal side of the protein of interest. (e.g., p. 4, entire page, last ¶ bridging to p. 5).

Therefore, it would have been obvious to substitute the His tag taught by the '337 patent with the native His tag, which has been known in the art, as taught by Tchaga et al. One of ordinary skill in the art would have been motivated to utilize the native His tag so as to expand the range of potential affinity markers that could be used to produce DNA templates via PCR as is taught by the '337 patent.

Given the skill in the art at the time of invention, it would have been routine to utilize PCR methods as taught by Lanar et al. and the '337 patent to produce DNA templates with the

native His tag sequence as taught by Tchaga et al., where the template could be expressed in a cell-free system and the nascent protein could be isolated/purified.

***Response to Arguments***

Applicant's arguments have been fully considered but they are not persuasive. Applicant's arguments are dependent upon arguments traversing what Lanar teaches under the 35 U.S.C. 102 rejection, which have been addressed. (Supra, Rejection No. 2). No additional arguments are presented. Therefore, this rejection is maintained.

***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

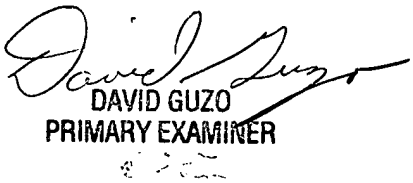
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766.

The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636



DAVID GUZO
PRIMARY EXAMINER